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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,146	09/16/2002	Wilhelm Amberg	51748	9829

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WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,146	AMBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-10* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/9/07 has been entered.

2. Claims 1-4 and 7-10 are pending.

3. Claims 1-3 and 7-9 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 4 and 10 are under examination as they read on an a pharmaceutical composition for the treatment or prevention of cardiovascular diseases comprising an ET_A endothelin blocker and an $\alpha v\beta 3$ integrin receptor antagonist and a trade package thereof.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* (all of record).

Kirchengast *et al* teach 8 endothelin blockers such as BQ 123, SB209670, BMS 182874, TAK 044, FR 139317, LU 135252, Bosentan, A 1277225 and LU135252 that were tested in different models of restenosis (a cardiovascular disorder) in rats and pigs. Kirchengast *et al* also teach that both the selective ET_A receptor antagonist FR 139317 and the mixed $ET_{A/B}$ receptor

antagonist TAK 044 were able to reduce neointima proliferation by 76% and 80%, respectively. Further, the balanced $ET_{A/B}$ receptor antagonist SB 209670 was shown to reduce the neointima/media ration by 52%. Furthermore, BMS 182874 and LU135252 were able to reduce neointima/media ration by 35% and 25%, respectively (see page 552 under Endothelin antagonism in experimental restenosis and table 1 in particular).

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition, comprising an endothelin blocker and an αvβ3 integrin receptor antagonist in claim 4.

However, Srivatsa *et al* teach that selective αvβ3 integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury (a cardiovascular disorder). Srivatsa *et al* also tested the effect of the XJ 735, a cyclic Arg-Gly-Asp (RGD) peptidomimetic αvβ3 antagonist on neointimal hyperplasia and lumen stenosis in a porcine coronary injury model (see age 424, 2nd col., at the end of the 2nd paragraph in particular). Srivatsa *et al* concluded that in large animal coronary stent restenosis model, use of a selective high affinity αvβ3 antagonist resulted in a marked reduction in neointimal hyperplasia and lumen stenosis (see page 426, last paragraph in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the endothelin blockers taught by Kirchegast *et al*, with the selective αvβ3 integrin antagonist XJ 735 taught by Srivatsa *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the endothelin blockers are able to reduce neointima proliferation (i.e., restenosis) as taught by Kirchengast *et al* and because the αvβ3 antagonist resulted in a marked reduction in neointimal hyperplasia the leading cause of restenosis. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 7/9/07, have been fully considered, but have not been found convincing.

Applicant traverses the rejection on the ground that the specifically claimed combination is not taught and it leads to a surprising effect. In particular, the present invention permits the use of each component at a dose less than the dose useful alone, with a reduction in side effects (page 4, lines 23-27 and page 20, lines 24-30). Applicant submits that there is no prior art cited and applied to support the proposition relied upon that co-administration of an endothelin blocker and αvβ3 integrin antagonist is expected to provide efficacy at lower doses than the doses used individually, with reduction in side effects.

The examiner notes that KSR reaffirmed its long-standing approach to determining whether a claimed invention that includes no new elements, but consists entirely of a "combination" of pre-existing elements, can properly be deemed to have been non-obvious subject matter at the time of its making. Under *Sakarida and Anderson's-black*, where an alleged invention consists of "an assembly of old elements," a court must inquire whether the claimed invention "only unites old elements with no change in their respective function," or whether the combined elements co-act with one another to produce some "new or different function" or an effect greater than the sum of the several effects taken separately." Sakraida, 425 U.S. at 60-61. The court states that if there is no such new or different function or effect, then the claimed subject matter is said to fail "the test of validity of combination patents," Sakraida, 425 U.S. at 282, and is deemed to have been obvious under 35 U.S.C 103 without the necessity of further analysis.

While Applicant's specification only asserts such surprising effect of the claimed combination without any evidence, Applicant request that the Examiner to cite specific art to support the proposition relied upon that that co-administration of an endothelin blocker and αvβ3 integrin antagonist is expected to provide efficacy at lower doses than the doses used individually, with reduction in side effects. However, when the ingredients are associated in an obvious manner set forth in the claims, they do not co-act with each other in any new or unexpected way and define nothing patentable over the prior art. Also the examiner notes that the critical date of extrinsic evidence, US 20060089374, showing a universal fact need not antedate the filing date. See MPEP § 2124. The examiner would like to draw Applicant's attention to work that was earlier than Applicant application for support of the Examiner's position that the combination therapy is expected to provide efficacy at lower doses than the doses used individually, with a reduction in side effects:

A) US. Patent No. 6,251,852 which teaches combination therapy for reducing the risks associated with cardiovascular disease. The `852 patent teaches that when administered as part of a combination therapy, the platelet aggregation inhibitor together with the HMG-CoA RI provide enhanced inhibition of platelet aggregation as compared to administration of either the HMG-CoA RI or the platelet aggregation inhibitor alone. Due to the greater benefit of the drug combination, lesser dosage amounts of the platelet aggregation inhibitor, and more particularly the GP IIa/IIIb receptor antagonist, may be needed to achieve the desired clinical result, thereby resulting in improved safety (see col., 4, lines 25-35).

B) US. Pat. No. 6,372,719 which teaches that combinations of αvβ3 integrin antagonists with chemotherapeutic agents are useful in treating and preventing neoplasia diseases. Preferably, the αvβ3 integrin antagonist agent or agents and the chemotherapeutic compounds, compositions, agents and therapies of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations for each of the individual components administered alone (see col., 11, lines 1-10).

C) McInnes GT, Clinical advantage of Valsartan, Cardiology 1999, 91:14-18 (abstract). McInnes teaches that Valsartan has additive effects with other antihypertensive drugs and combination therapy is effective in severe hypertension and in hypertension with renal insufficiency, where renal function is well maintained. Valsartan has good tolerability with a side-effect profile indistinguishable from placebo and superior to that of comparable drugs (see abstract).

D) Weir, M.R in Drugs Today 1998, 34(1):5 teaches that utilization of lower doses of tow or more agents may provide satisfactory reduction of blood pressure without the increased risk of adverse events with higher doses of the individual monotherapies. Moreover, there may be complimentary, additive, or even synergistic effects of two drugs working together by different mechanisms. Therefore, a low-dose therapeutic combination may represent an optimal approach, not only for patients unresponsive to higher doses of individual monotherapies, but perhaps also to initiate treatment (abstract).

E) Sugar et al in Antimicrobial, Agents and Chemotherapy, 1995 :598-601, teach that combination therapy with fluconazole and amphotericin B may achieve further improvements in efficacy and/or safety through the use of lower doses of amphotericin B without the loss of clinical response or with improved responses because the additive or synergistic effects of such combination therapy (see page 601, last ¶).

F) Walger et al in *Int Conf AIDS.* 1989 Jun 4-9; 5: 404 teach that a low-dose therapy with 800 mg AZT and 800 mg ACV seems to have similar positive effects on reduction of mortality and prevalence and severeness if opp. Inf. as standard AZT monotherapy. Toxicity seems to be reduced. Effects on compliance are positive (see abstract).

G) Furuhata *et al* in Gan To Kagaku Ryoho. 1999 Oct;26(11):1554-8 (English abstract) teach that low-dose FP and intermittent FP therapy might be fairly effective for advanced and unresectable colorectal carcinoma (see English Abstract).

H) Kobune K, in Res Commun Chem Pathol Pharmacol. 1991 Nov;74(2):153-65 (abstract) teach that the combination therapy with low-dose aspirin (81 mg/day) and warfarin is safe as an antithrombotic medication in heart valve replacement, and results in the inhibition of platelet functions without any side effect calling for special mention at the early unstable period after operation (abstract).

I) Waeber B in Current Hypertension Reports, 1996, 4(4) teaches that fixed low-dose combinations are very useful tools for treating hypertensive patients. Because of their simplicity of use, and the fact that they improve the blood pressure response rate while minimizing the incidence of adverse effects, such combinations are increasingly being considered as suitable for both second-line and first-line therapy (abstract).

Accordingly, the concept of combination therapy to lower doses and reduce side effects for effective treatment is known to the skilled in the art at the time the invention was made. Combination of the elements as claimed by known methods treating cardiovascular diseases with no change in their respective functions, and the combination that would have yielded predictable results to one of ordinary skill in the art at the time of the invention is deemed obvious by the prior art and not patentable. There is no invention when the effects of two compounds are simply added. The combination of the endothelin blockers and αvβ3 integrin antagonists added nothing to the expected characteristics of function of the claimed elements. The claimed combination of endothelin blockers and αvβ3 integrin antagonists is simply arranges old elements with each performing the same function it had been known to perform. Such combination adds nothing to the sum of useful knowledge where there is no change in the respective functions of the endothelin blockers and αvβ3 integrin antagonists in combination.

6. Claim 10 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* as applied to claims 4 above, and further in view of US Pat. No. 4,761,406 of record.

The teachings of Kirchengast *et al* and Srivatsa *et al* have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a trade package (kit) comprising as pharmaceutical agent, an endothelin blocker and an αvβ3 integrin receptor antagonist together with an instruction for use of the pharmaceutical agents in claim 10.

The `406 patent teaches kits which facilitate the necessary strict compliance with methods of treatments (e.g., see col., 1, lines 9-12; col., 2, lines 24-26, and columns 13-15 in particular).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the endothelin blocker such as BQ 123, SB209670, BMS 182874, TAK 044, FR 139317, LU 135252, Bosentan, A 1277225 and LU135252 taught by Kirchengast *et al* and αvβ3 integrin receptor antagonist such as XJ 735, a cyclic Arg-Gly-Asp (RGD) peptidomimetic taught by Srivatsa *et al* in a kit to facilitate the necessary strict compliance with methods of treatments

One would have been motivated to assemble the endothelin blocker and the αvβ3 integrin receptor antagonist in a kit format for conveniently and effectively implementing the method of treatment as taught by the `406 patent.

It is noted the only active ingredient in the claimed trade package (kit) is the endothelin blocker and the αvβ3 integrin receptor antagonist. Although the kits comprise instructions, there is no patentable weight given to the instructions themselves. It would have been prima facie obvious to the ordinary artisan to include a piece of paper in the kit identifying the components therein at the time the invention was made.

It is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a). Also, see In re Haller 73 USPQ 403 (CCPA 1947), where application of printed matter to old article cannot render article patentable and In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 7/9/07, have been fully considered, but have not been found convincing.

Applicant traverses the rejection for the reasons above.

However, based on the totality of the record as detailed above, the evidence of obviousness found in the combined reference teachings with Applicant's argument for nonobviousness. The Examiner concludes that the claimed invention encompassed by instant claims would have been obvious as a matter of law under 35 U.S.C 103(a).

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be

obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 10, 2007

Maher Haddad

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